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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,665	09/28/2000	Sudhirdas K. Prayaga	15966-572	8095

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/672,665	PRAYAGA ET AL.	
	Examiner	Art Unit	
	Anne M Wehbé	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *5-22,25-28,30,31,33,34,36-41 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,23,24,29,32,35 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the restriction/election requirement received on 4/29/02 has been entered. Applicant's election without traverse of the subject matter of group I, claims 1-4, 23-24, 29, 32, 35, and 42, and further the election of the species SEQ ID NO:2 is acknowledged. Claims 1-43 are pending in the instant application. Of these, claims 5-22, 25-28, 30-31, 33-34, 36-41, and 43 have been withdrawn from prosecution as being drawn to subject matter non-elected without traverse in paper no. 9. Claims 1-4, 23-24, 29, 32, 35, and 42 are currently under examination. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 23-24, 29, 32, 35, and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. The specification discloses isolated polypeptides comprising an amino acid sequence as set forth in SEQ ID NO: 2 or an amino acid sequence which differs from SEQ ID NO: 2 by no more than 15% of the amino acid residues, naturally occurring allelic variants of SEQ ID NO:2, pharmaceutical compositions comprising the disclosed polypeptides and methods of treating a pathology associated the polypeptide encoded by SEQ ID NO:2 using the disclosed pharmaceutical compositions or polypeptides.

The specification does not provide a sufficient written description for the scope of polypeptides encompassed by these claims. The specification discloses the isolation of a human cDNA , SEQ ID NO: 1, which contains an open reading frame comprising the amino acid sequence set forth in SEQ ID NO:2. The specification further discloses that SEQ ID NO:2 shares > approximately 91% sequence homology to a sequence previously reported as human prothymosin α.. The specification however fails to provide a sufficient description of a protein with the amino acid sequence of SEQ ID NO:2. The specification provides no description for any of the structural, physical, or biological properties of the putative protein corresponding to SEQ ID NO:2. Aside from the putative amino acid sequence, the specification provides no evidence that any polypeptide corresponding to the predicted amino acid sequence is in fact produced naturally in any type of cell or that the predicted protein product has any biological activity. The specification further fails to provide any guidance as to the characteristics of the putative protein such as cellular location, stability, half-life, or protein interactions such that allelic variants which share these properties can be identified. It is further noted that the specification fails to provide

any evidence that the putative protein corresponding to SEQ ID NO:2 is post-translationally processed to a "mature" form. In particular, the specification does not provide any guidance as to putative cleavage signals in the amino acid sequence of SEQ ID NO:2. The claims also read on variant polypeptides which differ from the amino acid sequence of SEQ ID NO:2 by up to 15% of the amino acid residues. Numerous amino acid sequences are possible which have 85% amino acid sequence identity with SEQ ID NO:2. The specification fails to describe which of the numerous sequences that have 85% or greater sequence homology to SEQ ID NO:2 actually correspond to an expressed or expressible protein, or describe any of the properties or characteristics of the numerous potential polypeptides encompassed by the scope of the claims.

In regards to the disclosed homology between SEQ ID NO:2 and human prothymosin α , the art at the time of filing teaches that the human prothymosin α gene family contains 6 known members. Of these, one gene contains introns and is expressed in two alternately spliced forms, whereas the other 5 are considered pseudogenes whose expression has not been conclusively established (Pineiro et al., (2000), Peptides, Vol. 21, 1433-1446). The 6 known prothymosin α genes are highly conserved and share greater than 95% sequence homology. Pineiro et al. also states that determination of pseudogene transcription and expression of the putative protein products of the pseudogenes is complicated by the degree of genomic conservation and apparent absence of size heterogeneity (Piniero et la., page 1436, column 2). Thus, based on the teachings of the art at the time of filing, the skilled artisan would not have been able to predict that a gene sequence with a high degree of homology to human prothymosin α would in fact encode a

functional human prothymosin α polypeptide. Furthermore, while the specification provides data from an RT-PCR assay which demonstrates the detection of mRNA transcripts in various cell types using PCR primers derived from SEQ ID NO:1, the specification provides no evidence that these mRNA are in fact translated into functional protein, or that the putative protein produced shares any of the properties or characteristics of human prothymosin α . Absent factual evidence, a percentage sequence similarity of less than 100% is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a known biomolecule with a similar sequence. It is known for nucleic acids as well as for proteins that even a single nucleotide or amino acid change or mutation can destroy or substantially change the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones will have a significant effect on structure, folding, activity etc. Therefore, the recitation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed polypeptides and the human prothymosin α protein in terms of biological properties and functions. Several publications document the unpredictability of attributing function based on sequence similarity. See in particular Gerhold et al. (1996) BioEssays, Vol. 18, No. 12, 973-981, Wells et al. (1997) J. Leuk. Biol., Vol. 61 (5), 545-550, and Russell et al. (1994) J. Mol. Biol., Vol. 244, 322-350. Thus, in the absence of any specific teachings in the specification concerning actual biological properties such as tissue distribution, expression, and function of polypeptides with 85% amino acid similarity or higher to SEQ ID NO:2, and in view of the art recognized unpredictability of attributing particular functional

properties to a polypeptide based on sequence similarity and the art recognized existence of untranslated pseudogenes with greater than 95% sequence homology to human prothymosin α , the specification fails to meet the requirements for written description under 35 U.S.C. 112, first paragraph.

The applicant is reminded that *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Please note as well that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-4, 23-24, 29, 32, 35, and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as claimed. The specification discloses isolated polypeptides comprising an amino acid sequence as set forth in SEQ ID NO:2 or an amino acid sequence which differs from SEQ ID NO:

2 by no more than 15% of the amino acid residues, naturally occurring allelic variants of SEQ ID NO:2, pharmaceutical compositions comprising the disclosed polypeptides and methods of treating a disease or a pathological condition associated with the SEQ ID NO:2 using the disclosed pharmaceutical compositions or polypeptides.

As noted above, the specification fails to provide sufficient guidance as to the structural and biological properties of the putative protein corresponding to SEQ ID NO:2, or provide guidance as to the structural, physical, or biological characteristics of polypeptides which differ from the amino acid sequence of SEQ ID NO:2 by as much as 15%. The specification further fails to identify amino acid residues of SEQ ID NO:2 or nucleic acid sequences of SEQ ID NO:1 which are either crucial or non-essential for the biological activity of the putative protein such that the skilled artisan could predict without undue experimentation which amino acids or nucleotides could be altered without affecting protein folding, stability, and biological activity.

Furthermore, while the specification notes the high degree of sequence similarity between the putative protein corresponding to SEQ ID NO:2 and human prothymosin α , and provides a working examples which demonstrates detection of mRNA in cells using primers derived from SEQ ID NO:1, the specification fails to provide any specific evidence that SEQ ID NO:1 encodes a protein corresponding to SEQ ID NO:2 or provide any specific guidance as to the particular biological activity of a putative protein encoded by SEQ ID NO:1, which is alleged to be the amino acid sequence of SEQ ID NO:2. The specification also fails to provide sufficient guidance that a protein corresponding to SEQ ID NO:2 shares any biological activity in common with

prothymosin α. At the time of filing, the art teaches that while the actual intracellular role of prothymosin α remains undefined, human prothymosin α may play a role in cellular proliferation and is capable of immunomodulatory activity (Piniero et al., page 1438, column 1). However, the specification provides no evidence that the polypeptide encoded by SEQ ID NO:1, or the amino acid sequence of SEQ ID NO:2 is capable of mediating any effect on cellular proliferation or capable of mediating any type of immunomodulatory activity. It is also noted that at the time of filing the art teaches that the human prothymosin α gene family contains numerous pseudogenes whose translation and function has not been conclusively demonstrated in cells either *in vitro* or *in vivo*. Thus, in view of the lack of guidance concerning any biological property of a protein corresponding to the amino acid sequence of SEQ ID NO:2 or encoded by SEQ ID NO:1, the absence of evidence in the specification that the amino acid sequence of SEQ ID NO:2 shares any biological activities in common with prothymosin α, the presence of numerous unexpressed pseudogenes in the prothymosin α gene family, the lack of guidance as to functional domains and amino acids critical for biological activity in the putative protein of SEQ ID NO:2, and the breadth of the claims, the skilled artisan at the time of filing would not have been able to predict whether a protein with an amino acid sequence corresponding to SEQ ID NO:2, or a protein with 85% or greater sequence identity with SEQ ID NO:2 would have any type of biological activity in cells *in vitro* or *in vivo*.

In addition, the specification fails to provide any guidance as to pathologies or diseases associated with the putative polypeptide corresponding to SEQ ID NO:2. Based on the known

activities of prothymosin α, the specification hypothesizes that polypeptides of the instant invention would be useful for treating conditions related to cellular proliferation, such as cancer. However, it is noted that neither the prior art nor the specification actually identifies any pathology or disease which is directly affected by the expression or lack of expression of any prothymosin α gene or protein. Further, as discussed in detail above, the specification fails to provide any evidence that a putative polypeptide corresponding to SEQ ID NO:2 actually shares any biological activity in common with prothymosin α. The specification also fails to provide any guidance for treating cancer using the putative protein corresponding to SEQ ID NO:2. The specification does not provide any guidance as to the properties or activities of the SEQ ID NO:2 polypeptide that would suggest that the addition of a polypeptide corresponding to SEQ ID NO:2 to cancer cells would result in any effect on cancer growth or metastasis. The applicant is reminded that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) . In the absence of specific information as to the actual biological properties of a polypeptide corresponding to SEQ ID NO:2 and the identity of diseases or conditions which are directly attributable to the expression or lack of expression of a polypeptide corresponding to SEQ ID NO:2, and in view of the lack of working examples demonstrating any therapeutic effect on any disease or pathology following the administration of a polypeptide corresponding to SEQ ID NO:2 and the breath of the claims, it would have required

undue experimentation for the skilled artisan to identify and treat any disease associated with the putative polypeptide corresponding to SEQ ID NO:2.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 35 provides for the use of the polypeptide according to claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 35 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 23-24, 29, 32, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,659,694 (Horecker) 4/21/87. The applicant claims an isolated polypeptide comprising a variant of an amino acid sequence as set forth in SEQ ID NO:2 wherein the variant does not differ from SEQ ID NO:5 by more than 15% of the amino acid residues. The applicant further claims said variant polypeptide wherein the variant comprises a conservative amino acid substitution. The applicant also claims a pharmaceutical composition comprising said polypeptide, and methods of using said polypeptides to treat pathologies or conditions associated with said polypeptide.

Horecker discloses the polypeptide sequence of both human and rat prothymosin α and its use as a pharmaceutical composition for protection against infection in mammals (Horecker, column 5, lines 40-60, and column14-16, claims 1-4). Both rat and human prothymosin α are > 85% identical to SEQ ID NO:2. It is further noted that human prothymosin α contain several conservative amino acid differences from SEQ ID NO:2, e.g. threonine to isoleucine. Thus, by teaching all the elements of the claims as written, Horecker anticipates the instant invention.

Claims 1, 4, 23-24, 29, 32, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,716,148 (Horecker) 11/29/87. The applicant claims an isolated

polypeptide comprising a variant of an amino acid sequence as set forth in SEQ ID NO:2 wherein the variant does not differ from SEQ ID NO:5 by more than 15% of the amino acid residues. The applicant further claims said variant polypeptide wherein the variant comprises a conservative amino acid substitution. The applicant also claims a pharmaceutical composition comprising said polypeptide, and methods of using said polypeptides to treat pathologies or conditions associated with said polypeptide.

Horecker discloses the polypeptide sequence of both human and rat prothymosin α and its use as a pharmaceutical composition for protection against infection in mammals and for reconstituting immune functions in thymic deprived or immunodeprived mammals (Horecker, column 5, lines 40-60, and column14-16, claims 1-4). Both rat and human prothymosin α are > 85% identical to SEQ ID NO:2. It is further noted that human prothymosin α contain several conservative amino acid differences from SEQ ID NO:2, e.g. threonine to isoleucine. Thus, by teaching all the elements of the claims as written, Horecker anticipates the instant invention.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries

should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé